



*Imaging Biomarkers in Radiation Oncology and Beyond:
Development, Evaluation and Clinical Translation*

Imaging Biomarker Roadmap for Cancer

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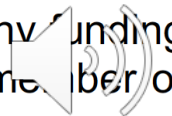
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Speaker Presentations - Funding Support, Disclosures, and Conflict of Interest Statement

Speakers **ARE REQUIRED** to include a slide in their PowerPoint presentation disclosing any funding support, disclosures, and conflicts of interest. The conflict may pertain to themselves, a member of their team, or an immediate family member.



BEST resource (2016)

Biomarker:

A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.

Molecular, histologic, radiographic or physiologic characteristics are types of biomarkers.

A biomarker is not an assessment of how an individual feels, functions, or survives.

Categories of biomarkers include:

- susceptibility/risk biomarker
- diagnostic biomarker
- monitoring biomarker
- prognostic biomarker
- predictive biomarker
- pharmacodynamic/response biomarker
- safety biomarker



BEST (Biomarkers, EndpointS, and other Tools) Resource

Authors

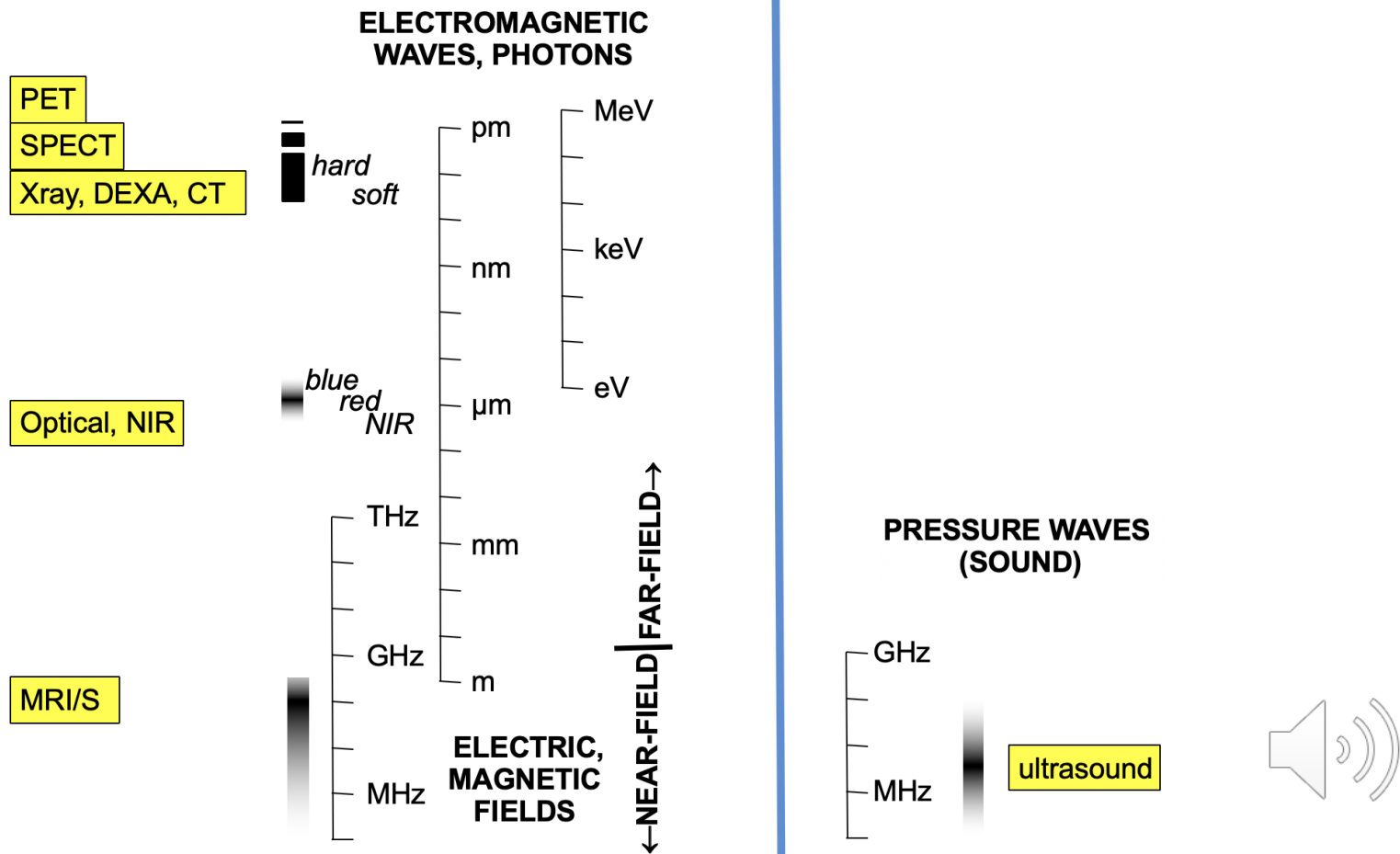
FDA-NIH Biomarker Working Group.


Silver Spring (MD): Food and Drug Administration (US); Bethesda (MD):

*Development of 1999 workshop
(Atkinson et al 2001)*



Six key cancer imaging modalities



Metrology definition	Colloquial definition	Examples
Ordered categorical (incl. binary)	How ugly?	
Extensive	How big?	
Intensive	How hot?	

Metrology definition	Colloquial definition	Examples
Ordered categorical (incl. binary)	How ugly?	<ul style="list-style-type: none"> TNM stage PET SPECT vis XR/CT MR us OR PET SPECT vis XR/CT MR us ACR BIRADS breast morphology XR ^{99m}Tc-etarfolatide FR+ SPECT Radiomic signature of heterogeneity CT
Extensive	How big?	<ul style="list-style-type: none"> LVEF SPECT MR us Spleen volume CT MR circumferential resection margin in rectal cancer MR
Intensive	How hot?	<ul style="list-style-type: none"> $\text{SUV}_{\max}^{111}\text{In}$-pentetreotide SPECT $\text{SUV}_{\max}^{18}\text{F}$-fludeoxyglucose PET Aprepitant receptor occupancy % PET ΔK^{trans} gadoterate MR DCE-US AUC us MRI ADC MR ^{13}C-pyruvate k_p MR



Problem statement: imaging biomarkers in cancer

- Not a new idea – predates molecular biology!
 - Tumour size: 1940s/50s
 - Tumor T_1 (1971) led to invention of MRI
 - Exemplified in FDA/NIH biomarker workshop (1999)
- Today used routinely – all BEST categories
 - Cancer drug development
 - Regulatory approval
 - Routine oncologic practice
- Many investigational imaging biomarkers in cancer
 - Disappointing rate of translation – why?



“...molecular, histologic, radiographic, or physiologic characteristics...”

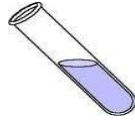
Biospecimen removed from patient

molecule or cell analyte detected with *in vitro* Diagnostic Device

genetics
soluble biomarkers
immunohistochemistry
in situ hybridisation
genomics
proteomics
metabolomics
cytology
microbiology
erythrocyte sedimentation
etc

biofluids

urine
blood
exhalate
sputum
saliva
semen
faeces
synovial fluid
CSF
etc



solid tissues

cervical smear
skin biopsy
hair follicle
buccal biopsy
liver biopsy
bone biopsy
synovial biopsy
tumour biopsy
excised tumour
etc



Biosignal measured in vivo

signals detected by *in vivo* Diagnostic Device

electromagnetic fields & photons

PET
SPECT
CT, XR
endoscopy
fluorescence
MRI/S
ECG
EEG
MEG
etc



sound & pressure

ultrasound
infrasound
palpation
auscultation
plethysmography
spirometry
etc

imaging
electrophysiology
physiologic measurement
wearables/smartphones
etc



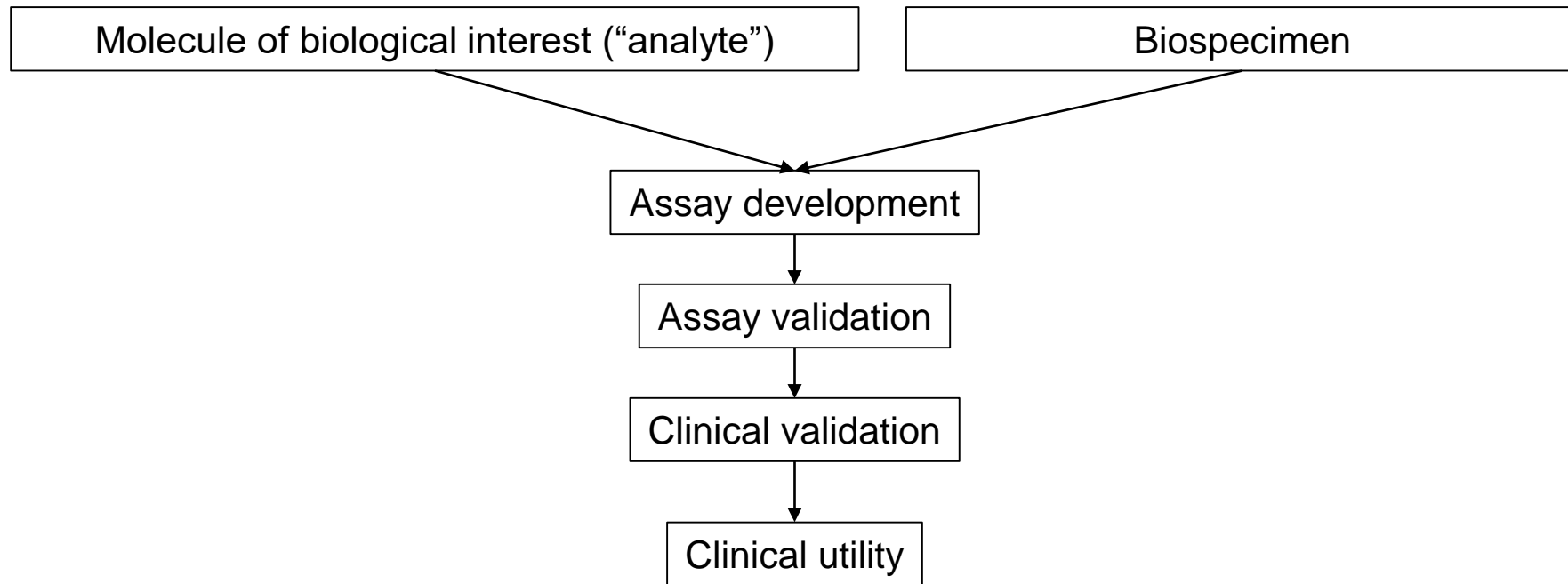
**Imaging biomarker:
Scanner in hospital Radiology Dept**

**Biospecimen biomarker:
In vitro diagnostic device**

Different scanners from different vendors installed in different hospitals	Identical IVDDs
Scanners not designed, maintained or approved for measuring biomarkers	IVDDs designed, maintained and approved for specific measurement
Main job role not quantitation	Trained, dedicated staff
Quality depends mainly on events at the moment of scanning	Quality depends mainly on the central lab
Picture quality drives innovation: unpredictable effect on quantitation	Stable platform due to regulatory approval
Seldom defined analytes	Defined molecular entity via analytical biochemistry



Typical biospecimen biomarker validation roadmap



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<http://dx.doi.org/10.1038/nrclinonc.2016.162>

Includes supplementary files

- Problem statement
- Examples – all modalities and contexts of use
- Definitions
- Detailed roadmap
- Recommendations

OPEN

Imaging biomarker roadmap for cancer studies

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Abstract | Imaging biomarkers (IBs) are integral to the routine management of patients with cancer. IBs used daily in oncology include clinical TNM stage, objective response and left ventricular ejection fraction. Other CT, MRI, PET and ultrasonography biomarkers are used



Figure 2 The imaging biomarker roadmap

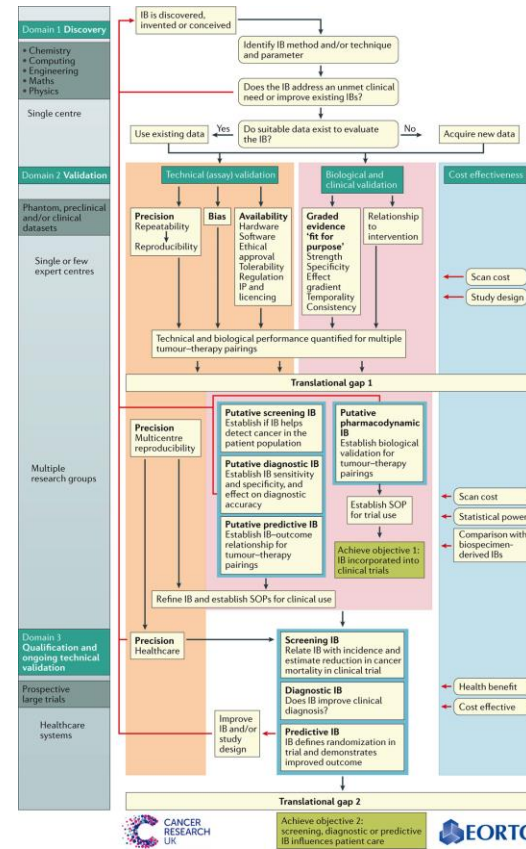
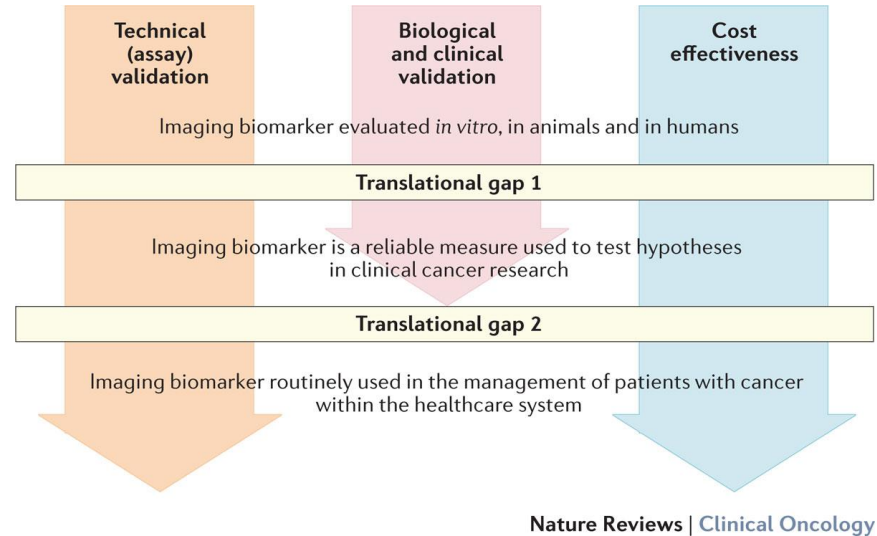


Figure 1 Overview of the imaging biomarker roadmap



Key perspectives

	Imaging (biosignal) bm	Typical biospecimen bm
Technical validation, clinical validation, clinical utility	Iterative in parallel	Mainly in series
Biological and clinical validity	Biological validation platform of evidence e.g. Bradford Hill criteria	Definitive clinical outcome studies e.g. Kaplan Meier



Roadmap recommendations

1. Align grants and publications to roadmap
2. Exhaustively document methodology in publications
- 3-7. Technical (assay validation)

Consensus, accreditation, repeatability, reproducibility, analysis methodology

- 8-11. Biological and clinical validation

Platform of evidence (Bradford Hill criteria)

Imaging-pathology correlation (human and animal)

Data sharing

Publication bias

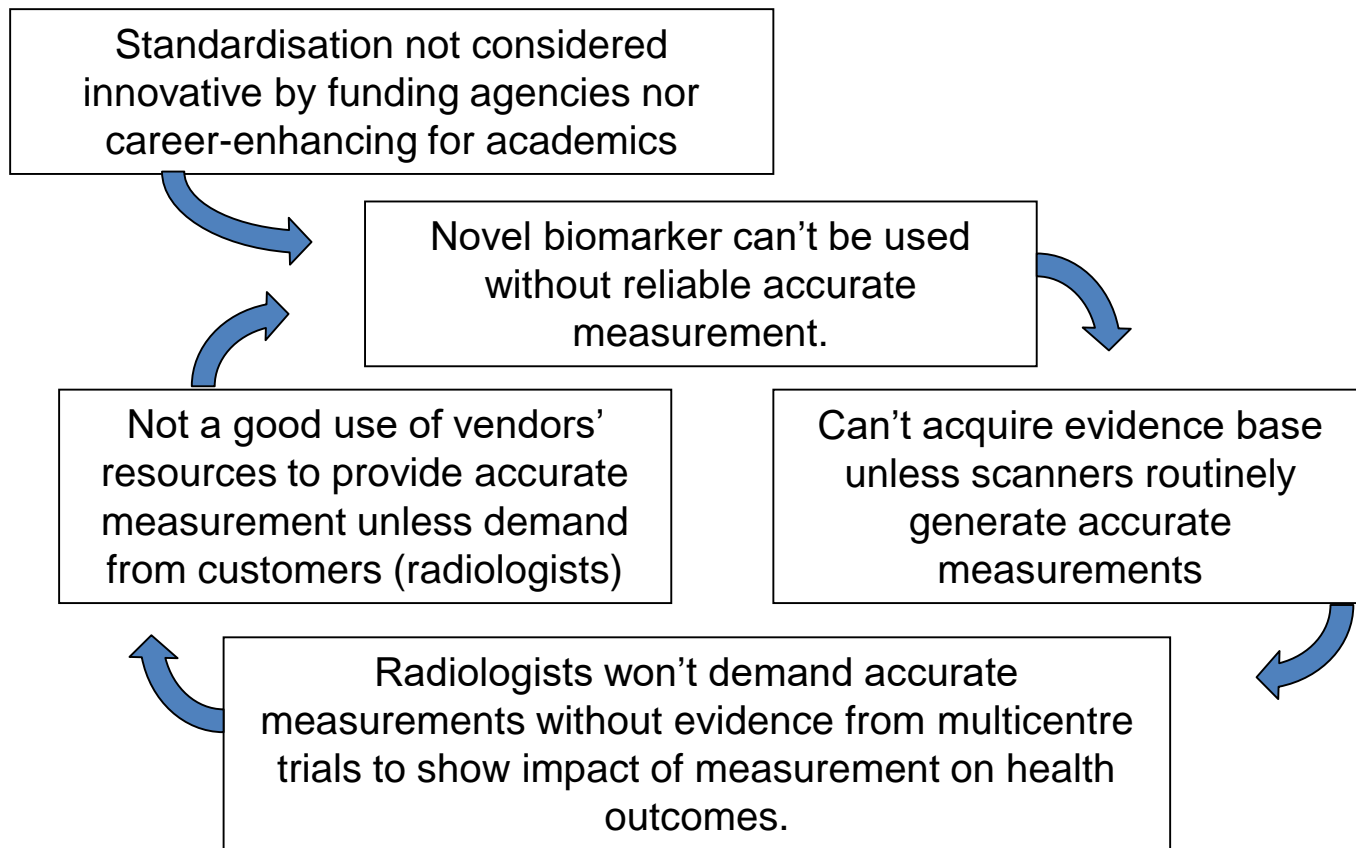
12. Design of outcome studies

- 13-14. Cost effectiveness and clinical utility

Imaging agents pricing; QALY advantage



The problem of poorly aligned incentives



Innovative approaches to incentivisation

Incentivisation through public-private partnerships, professional bodies

- Standardising FDG-PET, FLT-PET, MRI-ADC, MRI- K^{trans} , MRI-DIILD etc



Academics innovate, businesses standardise



